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GLP DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel derivatives of human glucagon-like peptides (GLP), in particular glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2) and fragments thereof and analogues of such fragments which have a protracted profile of action and to methods of making and using them.

BACKGROUND OF THE INVENTION

Polypeptides are widely used in medical practice, and since they can be produced by recombinant DNA technology it can be expected that their importance will increase also in the years to come. When native polypeptides or analogues thereof are used in therapy it is generally found that they have a high clearance. A high clearance of a therapeutic agent is inconvenient in cases where it is desired to maintain a high blood level thereof over a prolonged period of time since repeated administrations will then be necessary. Examples of polypeptides which have a high clearance are: ACTH, corticotropin-releasing factor, angiotensin, calcitonin, insulin, glucagon, glucagon-like peptide-1, glucagon-like peptide-2, insulin-like growth factor-1, insulin-like growth factor-2, gastric inhibitory peptide, growth hormone-releasing factor, pituitary adenylate cyclase activating peptide, secretin, enterogastrin, somatostatin, somatotropin, somatomedin, parathyroid hormone, thrombopoietin, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, oxytocin, opiods and analogues thereof, superoxide dismutase, interferon, asparaginase, arginase, arginine deaminase, adenosine deaminase and ribonuclease. In some cases it is possible to influence the release profile of polypeptides by applying suitable pharmaceutical compositions, but this approach has various shortcomings and is not generally applicable.

The amino acid sequence of GLP-1 and GLP-2 is given *i.a.* by Schmidt *et al.* (*Diabetologia* **28** 704-707 (1985). Although the interesting pharmacological properties of the fragment of glucagon-like peptide-1 known as GLP-1 (7-37) and analogues thereof and also the properties of GLP-2 and fragments and analogues thereof have attracted much attention in recent years only little is known about the structure of these molecules. The secondary structure of GLP-1 in micelles has been described by Thorton *et al.* (*Biochemistry* **33** 3532-3539 (1994)), but a tertiary structure can not be ascribed to the molecule, and GLP-1 and GLP-2 are indeed very flexible molecules. GLP-1 and analogues of GLP-1 and fragments thereof are potentially useful *i.a.* in the treatment of type 1 and type 2 diabetes and GLP-2 and fragments thereof and analogues of GLP-2 and fragments thereof are potentially useful *i.a.* in regulation of appetite and in the treatment of small bowel syndrome. However, the high clearance limits the usefulness of these compounds, and thus there still is a need for improvements in this field.

SUMMARY OF THE INVENTION

GLP-1 and GLP-2 originate from preproglucagon which is synthesized *i.a.* in the L-cells in the distal illeum, in the pancreas and in the brain. Processing of preproglucagon to give GLP-1 and GLP-2 occurs mainly in the L-cells. Human GLP-1 is a 37 amino acid residue peptide and GLP-2 is a 34 amino acid residue peptide. A simple system is used to describe fragments and analogues of these peptides. Thus, for example, Gly^{8}-GLP-1(7-37) designates a fragment of GLP-1 formally derived from GLP-1 by deleting the amino acid residues Nos. 1 to 6 and substituting the naturally occurring amino acid residue in position 8 (Ala) by Gly. Similarly, $Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37) designates GLP-1(7-37) wherein the ε-amino group of the Lys residue in position 34 has been tetradecanoylated. Where reference in this text is made to C-terminally extended GLP-1 analogues, the amino acid residue in position 38 is Arg unless otherwise indicated, the optional amino acid residue in position 39 is also Arg unless otherwise indicated and the optional amino acid residue in position 40 is Asp unless otherwise indicated.

In its broadest aspect, the present invention relates to derivatives of GLP-1 and GLP-2 and analogues thereof. The derivatives according to the invention have interesting pharmacological properties, in particular they have a more protracted profile of action than the parent peptides.

In the present text, the designation "an analogue" is used to designate a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide.

The term "derivative" is used in the present text to designate a peptide in which one or more of the amino acid residues have been chemically modified, *e.g.* by alkylation, acylation, ester formation or amide formation.

The term "a GLP derivative" is used in the present text to designate a derivative of GLP-1 or an analogue thereof or of GLP-2 or an analogue thereof. In the present text, the parent peptide from which such a derivative is formally derived is in some places referred to as the "GLP moiety" of the derivative.

In a preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent attached to any one amino acid residue with the proviso that only if the substituent has an ω-carboxylic acid group or is an alkyl group can it be attached to the N-terminal or C-terminal amino acid residue of the parent polypeptide.

In another preferred embodiment, the present invention relates to a GLP derivative wherein the lipophilic substituent comprises from 4 to 40 carbon atoms, more preferred from 8 to 25 carbon atoms.

In a further preferred embodiment, the present invention relates to a GLP derivative wherein a lipophilic substituent is attached to an amino acid residue in such a way that a carboxyl group of the lipophilic substituent forms an amide bond with an amino group of the amino acid residue.

In a further preferred embodiment, the present invention relates to a GLP derivative wherein a lipophilic substituent is attached to an amino acid residue in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid residue.

In a further preferred embodiment, the present invention relates to a GLP derivative wherein a lipophilic substituent is attached to the parent polypeptide by means of a spacer.

In a further preferred embodiment, the present invention relates to a GLP derivative wherein a lipophilic substituent is attached to the parent polypeptide by means of a spacer which is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, preferably two methylene groups which spacer forms a bridge between an amino group of the parent polypeptide and an amino group of the lipophilic substituent.

In a further preferred embodiment, the present invention relates to a GLP derivative wherein a lipophilic substituent is attached to the parent polypeptide by means of a spacer which is an amino acid residue except Cys, or a dipeptide such as Gly-Lys.

In a further preferred embodiment, the present invention relates to a GLP derivative wherein a lipophilic substituent is attached to the parent polypeptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys and wherein a carboxyl group of the parent polypeptide forms an amide bond with an amino group of a Lys residue or a dipeptide containing a Lys residue, and the other amino group of the Lys residue or a dipeptide containing a Lys residue forms an amide bond with a carboxyl group of the lipophilic substituent.

In a further preferred embodiment, the present invention relates to a GLP derivative wherein a lipophilic substituent is attached to the parent polypeptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys and wherein an amino group of the parent polypeptide forms an amide bond with a carboxylic group of the amino acid or dipeptide spacer, and an amino group of the amino acid or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

In a further preferred embodiment, the present invention relates to a GLP derivative wherein a lipophilic substituent is attached to the parent polypeptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys and wherein a carboxyl group of the parent polypeptide forms an amide bond with an amino group of the amino acid or dipeptide spacer, and the carboxyl group of the amino acid or dipeptide spacer forms an amide bond with an amino group of the lipophilic substituent.

In a further preferred embodiment, the present invention relates to a GLP derivative wherein a lipophilic substituent is attached to the parent polypeptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys, and wherein a carboxyl group of the parent polypeptide forms an amide bond with an amino group of Asp or Glu, or a dipeptide containing an Asp or Glu residue, and a carboxyl group of the spacer forms an amide bond with an amino group of the lipophilic substituent.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is a straight-chain or branched alkyl group.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is the acyl group of a straight-chain or branched fatty acid.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is an acyl group selected from the group comprising $CH_3(CH_2)_nCO$-, wherein n is 4 to 38, preferably $CH_3(CH_2)_6CO$-, $CH_3(CH_2)_8CO$-, $CH_3(CH_2)_{10}CO$-, $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is an acyl group selected from the group comprising $HOOC(CH_2)_mCO$-, wherein m is 4 to 38, preferably $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- and $HOOC(CH_2)_{22}CO$-.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is a group of the formula $CH_3(CH_2)_p((CH_2)_qCOOH)CHNH$-$CO(CH_2)_2CO$-, wherein p and q are integers and p+q is an integer of from 8 to 40, preferably from 12 to 35.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is a group of the formula $CH_3(CH_2)_rCO$-$NHCH(COOH)(CH_2)_2CO$-, wherein r is an integer of from 10 to 24.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is a group of the formula $CH_3(CH_2)_sCO$-$NHCH((CH_2)_2COOH)CO$-, wherein s is an integer of from 8 to 24.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is a group of the formula $COOH(CH_2)_tCO$- wherein t is an integer of from 8 to 24.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is a group of the formula -$NHCH(COOH)(CH_2)_4NH$-$CO(CH_2)_uCH_3$, wherein u is an integer of from 8 to 18.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is a group of the formula -NHCH(COOH)$(CH_2)_4$NH-COCH($(CH_2)_2$COOH)NH-CO$(CH_2)_w CH_3$, wherein w is an integer of from 10 to 16.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is a group of the formula -NHCH(COOH)$(CH_2)_4$NH-CO$(CH_2)_2$CH(COOH)NH-CO$(CH_2)_x CH_3$, wherein x is an integer of from 10 to 16.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which is a group of the formula -NHCH(COOH)$(CH_2)_4$NH-CO$(CH_2)_2$CH(COOH)NHCO$(CH_2)_y CH_3$, wherein y is zero or an integer of from 1 to 22.
In a further preferred embodiment, the present invention relates to a GLP derivative which has one lipophilic substituent.

In a further preferred embodiment, the present invention relates to a GLP derivative which has two lipophilic substituents.

In a further preferred embodiment, the present invention relates to a GLP derivative in which the C-terminal amino acid residue is present in the form of the amide.

In a further preferred embodiment, the present invention relates to a GLP derivative having a lipophilic substituent which can be negatively charged.

In a further preferred embodiment, the present invention relates to a GLP derivative the parent polypeptide of which is selected from the group comprising GLP-1(1-45) or an analogue thereof.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative derived from a GLP-1 fragment selected from the group comprising GLP-1(7-35), GLP-1(7-36), GLP-1(7-36)amide, GLP-1(7-37), GLP-1(7-38), GLP-1(7-39), GLP-1(7-40) and GLP-1(7-41) or an analogue thereof.

In a further preferred embodiment, the present invention relates to a GLP-1 analogue derived from a GLP-1 analogue selected from the group comprising GLP-1(1-35), GLP-1(1-36), GLP-1(1-36)amide, GLP-1(1-37), GLP-1(1-38), GLP-1(1-39), GLP-1(1-40) and GLP-1(1-41) or an analogue thereof..

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the designation analogue comprises derivatives wherein a total of up to fifteen, preferably up to ten amino acid residues have been exchanged with any α-amino acid residue.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent polypeptide is selected from the group comprising Arg^{26}-GLP-1(7-37), Arg^{34}-GLP-1(7-37), Lys^{36}-GLP-1(7-37), $Arg^{26,34}Lys^{36}$-GLP-1(7-37), $Arg^{26}Lys^{36}$-GLP-1(7-37), $Arg^{34}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26}$-GLP-1(7-37), $Gly^{8}Arg^{34}$-GLP-1(7-37), $Gly^{8}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-37) and $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-37).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent polypeptide is selected from the group comprising $Arg^{26}Lys^{38}$-GLP-1(7-38), $Arg^{26,34}Lys^{36,38}$-GLP-1(7-38), $Gly^{8}Arg^{26}Lys^{38}$-GLP-1(7-38) and $Gly^{8}Arg^{26,34}Lys^{36,38}$-GLP-1(7-38).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent polypeptide is selected from the group comprising $Arg^{26}Lys^{39}$-GLP-1(7-39), $Arg^{26,34}Lys^{36,39}$-GLP-1(7-39), $Gly^{8}Arg^{26}Lys^{39}$-GLP-1(7-39) and $Gly^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent polypeptide is selected from the group comprising $Arg^{34}Lys^{40}$-GLP-1(7-40), $Arg^{26,34}Lys^{36,40}$-GLP-1(7-40), $Gly^{8}Arg^{34}Lys^{40}$-GLP-1(7-40) and $Gly^{8}Arg^{26,34}Lys^{36,40}$-GLP-1(7-40).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative which is selected from the group comprising

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-37);
Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-37);
Arg^{26},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);
$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);
$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-38);
Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);
Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);
Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-38);
Arg^{26},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);
$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);
$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);
$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-39);
Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);
Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);
Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-39);
Arg^{26},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);
$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);
$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);
$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-40);
Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);
Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);
Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Gly^{8},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Gly^{8},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-37);

Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-37);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-38);

Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-38);

$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-38);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-38);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-39);

Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-39);

$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-39);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-39);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-40);

$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},Arg^{26},$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-37);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-38);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-39);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-40);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36)amide;

Arg^{26},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8},Arg^{26},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-37);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-37);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-37);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

Gly^{8},Arg^{26},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-38);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-38);

$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

Gly^{8},$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-38);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-38);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-38);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-39);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-39);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-39);

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-39);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-39);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-39);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-40);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-40);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-40);

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-40);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-40);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36);

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-35);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-35);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-35);

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-35);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-35);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(choloyl)),Arg^{34}-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(choloyl)),Arg^{34}-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-38);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-38);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(choloyl)),Arg^{34}-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-39);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-39);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(choloyl)),Arg^{34}-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-40);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-40);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(lithocholoyl)),Arg^{34}-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-38);
Lys^{26}(N^{ε}-(lithocholoyl)),Arg^{34}-GLP-1(7-38);
Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))Arg^{34}-GLP-1(7-38);
$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-38);
Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-38);
Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-39);
Lys^{26}(N^{ε}-(lithocholoyl)),Arg^{34}-GLP-1(7-39);
Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))Arg^{34}-GLP-1(7-39);
$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-39);
Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-39);
Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-40);
Lys^{26}(N^{ε}-(lithocholoyl)),Arg^{34}-GLP-1(7-40);
Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))Arg^{34}-GLP-1(7-40);
$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-40) and
Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-40).

In a further preferred embodiment, the present invention relates to a GLP derivative the parent polypeptide of which is selected from the group comprising GLP-2(1-35) or an analogue thereof.

In a further preferred embodiment, the present invention relates to a GLP-2 derivative derived from a GLP-2 fragment selected from the group comprising GLP-2(1-30), GLP-2(1-31), GLP-2(1-32), GLP-2(1-33), GLP-2(1-34) and GLP-2(1-35).

In a further preferred embodiment, the present invention relates to a GLP-2 derivative wherein the designation analogue comprises derivatives wherein a total of up to ten amino acid residues have been exchanged with any α-amino acid residue.

In a further preferred embodiment, the present invention relates to a GLP-2 derivative wherein the parent polypeptide is selected from the group comprising Lys^{20}-GLP-2(1-33) and Lys^{20},Arg^{30}-GLP-2(1-33).

In a further preferred embodiment, the present invention relates to a GLP-2 derivative wherein the parent polypeptide is Arg^{30},Lys^{34}-GLP-2(1-34).

In a further preferred embodiment, the present invention relates to a GLP-2 derivative wherein the parent polypeptide is selected from the group comprising Arg^{30},Lys^{35}-GLP-2(1-35), $Arg^{30,35}$,Lys^{20}-GLP-2(1-35) and Arg^{35}-GLP-2(1-35).

In a further preferred embodiment, the present invention relates to a GLP-2 derivative which is selected from the group comprising

$Lys^{20}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-33);
$Lys^{20,30}$-bis(N^{ε}-tetradecanoyl)-GLP-2(1-33);
$Lys^{20}(N^{\varepsilon}$-tetradecanoyl),Arg^{30}-GLP-2(1-33);
Arg^{30},$Lys^{35}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-35);
$Arg^{30,35}$,$Lys^{20}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-35);
Arg^{35},$Lys^{30}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-35);
Arg^{30},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-34);
$Lys^{20}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-2(1-33);
$Lys^{20,30}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-2(1-33);
$Lys^{20}(N^{\varepsilon}$-(ω-carboxynonadecanoyl)),Arg^{30}-GLP-2(1-33);
Arg^{30},$Lys^{35}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-2(1-35);
$Arg^{30,35}$,$Lys^{20}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-2(1-35);
Arg^{35},$Lys^{30}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-2(1-35); and
Arg^{30},$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-2(1-34).

In a further preferred embodiment, the present invention relates to a pharmaceutical composition comprising a GLP derivative and a pharmaceutically acceptable vehicle or carrier.

In a further preferred embodiment, the present invention relates to the use of a GLP derivative according to the invention for the preparation of a medicament which has a more protracted

action than the parent polypeptide.

In a further preferred embodiment, the present invention relates to the use of a GLP-1 derivative according to the invention for the preparation of a medicament with protracted effect for the treatment of non-insulin dependent diabetes mellitus.

In a further preferred embodiment, the present invention relates to the use of a GLP-1 derivative according to the invention for the preparation of a medicament with protracted effect for the treatment of insulin dependent diabetes mellitus.

In a further preferred embodiment, the present invention relates to the use of a GLP-1 derivative according to the invention for the preparation of a medicament with protracted effect for the treatment of obesity.

In a further preferred embodiment, the present invention relates to the use of a GLP-2 derivative according to the invention for the preparation of a medicament with protracted effect for the treatment of obesity.

In a further preferred embodiment, the present invention relates to the use of a GLP-2 derivative according to the invention for the preparation of a medicament with protracted effect for the treatment of small bowel syndrome.

DETAILED DESCRIPTION OF THE INVENTION

To obtain a satisfactory protracted profile of action of the GLP derivative the lipophilic substituent attached to the GLP moiety preferably comprises 4-40 carbon atoms, in particular 8-25 carbon atoms. The lipophilic substituent may be attached to an amino group of the GLP moiety by means of a carboxyl group of the lipophilic substituent which forms an amide bond with an amino group of the amino acid to which it is attached. Conversely, lipophilic substituent

may be attached to said amino acid in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid. As an alternative, the lipophililic substituent may be linked to the GLP moiety via an ester bond. Formally, the ester can be formed either by reaction between a carboxyl group of the GLP moiety and a hydroxyl group of the substituent-to-be or by reaction between a hydroxyl group of the GLP moiety and a carboxyl group of the substituent-to-be. As a further alternative, the lipophilic substituent can be an alkyl group which is introduced into a primary amino group of the GLP moiety.

In one preferred embodiment of the invention, the lipophilic substituent is attached to the GLP moiety by means of a spacer in such a way that a carboxyl group of the spacer forms an amide bond with an amino group of the GLP moiety. Examples of suitable spacers are succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys. When the spacer is succinic acid, one carboxyl group thereof may form an amide bond with an amino group of the amino acid, and the other carboxyl group thereof may form an amide bond with an amino group of the lipophilic substituent. When the spacer is Lys, Glu or Asp, the carboxyl group thereof may form an amide bond with an amino group of the amino acid, and the amino group thereof may form an amide bond with a carboxyl group of the lipophilic substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the ε-amino group of Lys and the lipophilic substituent. In one preferred embodiment, such a further spacer is succinic acid which forms an amide bond with the ε-amino group of Lys and with an amino group present in the lipophilic substituent. In another preferred embodiment such a further spacer is Glu or Asp which forms an amide bond with the ε-amino group of Lys and another amide bond with a carboxyl group present in the lipophilic substituent, that is, the lipophilic substituent is a N^{ε}-acylated lysine residue.

In another preferred embodiment of the present invention, the lipophilic substituent has a group which can be negatively charged. One preferred group which can be negatively charged is a carboxylic acid group.

The parent polypeptide can be produced by a method which comprises culturing a host cell

containing a DNA sequence encoding the polypeptide and capable of expressing the polypeptide in a suitable nutrient medium under conditions permitting the expression of the polypeptide, after which the resulting polypeptide is recovered from the culture.

The medium used to culture the cells may be any conventional medium suitable for growing the host cells, such as minimal or complex media containing appropriate supplements. Suitable media are available from commercial suppliers or may be prepared according to published recipes (*e.g.* in catalogues of the American Type Culture Collection). The polypeptide produced by the cells may then be recovered from the culture medium by conventional procedures including separating the host cells from the medium by centrifugation or filtration, precipitating the proteinaceous components of the supernatant or filtrate by means of a salt, *e.g.* ammonium sulphate, purification by a variety of chromatographic procedures, *e.g.* ion exchange chromatography, gelfiltration chromatography, affinity chromatography, or the like, dependent on the type of polypeptide in question.

The DNA sequence encoding the parent polypeptide may suitably be of genomic or cDNA origin, for instance obtained by preparing a genomic or cDNA library and screening for DNA sequences coding for all or part of the polypeptide by hybridization using synthetic oligonucleotide probes in accordance with standard techniques (see, for example, Sambrook, J, Fritsch, EF and Maniatis, T, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, New York, 1989). The DNA sequence encoding the polypeptide may also be prepared synthetically by established standard methods, *e.g.* the phosphoamidite method described by Beaucage and Caruthers, *Tetrahedron Letters* **22** (1981), 1859 - 1869, or the method described by Matthes *et al.*, *EMBO Journal* **3** (1984), 801 - 805. The DNA sequence may also be prepared by polymerase chain reaction using specific primers, for instance as described in US 4,683,202 or Saiki *et al.*, *Science* **239** (1988), 487 - 491.

The DNA sequence may be inserted into any vector which may conveniently be subjected to recombinant DNA procedures, and the choice of vector will often depend on the host cell into which it is to be introduced. Thus, the vector may be an autonomously replicating vector, *i.e.* a

vector which exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, *e.g.* a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated.

The vector is preferably an expression vector in which the DNA sequence encoding the polypeptide is operably linked to additional segments required for transcription of the DNA, such as a promoter. The promoter may be any DNA sequence which shows transcriptional activity in the host cell of choice and may be derived from genes encoding proteins either homologous or heterologous to the host cell. Examples of suitable promoters for directing the transcription of the DNA encoding the polypeptide of the invention in a variety of host cells are well known in the art, cf. for instance Sambrook *et al.*, *supra*.

The DNA sequence encoding the polypeptide may also, if necessary, be operably connected to a suitable terminator, polyadenylation signals, transcriptional enhancer sequences, and translational enhancer sequences. The recombinant vector of the invention may further comprise a DNA sequence enabling the vector to replicate in the host cell in question.

The vector may also comprise a selectable marker, *e.g.* a gene the product of which complements a defect in the host cell or one which confers resistance to a drug, *e.g.* ampicillin, kanamycin, tetracyclin, chloramphenicol, neomycin, hygromycin or methotrexate.

To direct a parent polypeptide of the present invention into the secretory pathway of the host cells, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) may be provided in the recombinant vector. The secretory signal sequence is joined to the DNA sequence encoding the polypeptide in the correct reading frame. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the polypeptide. The secretory signal sequence may be that normally associated with the polypeptide or may be from a gene encoding another secreted protein.

The procedures used to ligate the DNA sequences coding for the present polypeptide, the promoter and optionally the terminator and/or secretory signal sequence, respectively, and to insert them into suitable vectors containing the information necessary for replication, are well known to persons skilled in the art (cf., for instance, Sambrook *et al.*, *supra*).

The host cell into which the DNA sequence or the recombinant vector is introduced may be any cell which is capable of producing the present polypeptide and includes bacteria, yeast, fungi and higher eukaryotic cells. Examples of suitable host cells well known and used in the art are, without limitation, *E. coli*, *Saccharomyces cerevisiae*, or mammalian BHK or CHO cell lines.

Compounds which can be useful as GLP-1 moieties according to the present invention are described in International Patent Application No. WO 87/06941 (The General Hospital Corporation) which relates to a peptide fragment which comprises GLP-1(7-37) and functional derivatives thereof and to its use as an insulinotropic agent.

Further GLP-1 analogues are described in International Patent Application No. 90/11296 (The General Hospital Corporation) which relates to peptide fragments which comprise GLP-1(7-36) and functional derivatives thereof and have an insulinotropic activity which exceeds the insulinotropic activity of GLP-1(1-36) or GLP-1(1-37) and to their use as insulinotropic agents.

International Patent Application No. 91/11457 (Buckley *et al.*) discloses analogues of the active GLP-1 peptides 7-34, 7-35, 7-36, and 7-37 which can also be useful as GLP-1 moieties according to the present invention.

Pharmaceutical compositions

Pharmaceutical compositions containing a polypeptide derivative according to the present invention may be administered parenterally to patients in need of such a treatment. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by

means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. A further option is a composition which may be a powder or a liquid for the administration of the polypeptide derivative in the form of a nasal or pulmonal spray. As a still further option, the polypeptide derivatives of the invention can also be administered transdermally, *e.g.* from a patch, optionally a iontophoretic patch.

Pharmaceutical compositions containing a polypeptide derivative of the present invention may be prepared by conventional techniques, *e.g.* as described in Remington's Pharmaceutical Sciences, 1985.

Thus, the injectable compositions of the polypeptide derivative of the invention can be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the ingredients as appropriate to give the desired end product.

Thus, according to one procedure, the polypeptide derivative is dissolved in an amount of water which is somewhat less than the final volume of the composition to be prepared. An isotonic agent, a preservative and a buffer is added as required and the pH value of the solution is adjusted - if necessary - using an acid, *e.g.* hydrochloric acid, or a base, *e.g.* aqueous sodium hydroxide as needed. Finally, the volume of the solution is adjusted with water to give the desired concentration of the ingredients.

Examples of isotonic agents are sodium chloride, mannitol and glycerol.

Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate and benzyl alcohol.

Examples of suitable buffers are sodium acetate and sodium phosphate.

A composition for nasal administration of certain polypeptides may, for example, be prepared as described in European Patent No. 272097 (to Novo Nordisk A/S) or in WO 93/18785.

According to some embodiments of the present invention, the GLP-1 derivative is provided in the form of an injectable solution. In such embodiments, the solutions preferably contain not less than about 2 mg/ml, preferably not less than about 5 mg/ml, more preferred not less than about 10 mg/ml of the GLP-1 derivative and, preferably, not more than about 100 mg/ml of the GLP-1 derivative.

The polypeptide derivatives of this invention can be used in the treatment of various diseases. The particular polypeptide derivative to be used and the optimal dose level for any patient will depend on the disease to be treated and on a variety of factors including the efficacy of the specific peptide derivative employed, the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity of the case. It is recommended that the dosage of the polypeptide derivative of this invention be determined for each individual patient by those skilled in the art in a similar way as for known parent polypeptides.

In particular, it is envisaged that the derivatized GLP-1 derivative will be useful for the preparation of a medicament with protracted action/effect for the treatment of non-insulin dependent diabetes mellitus and/or for the treatment of obesity.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realizing the invention in diverse forms thereof.

EXAMPLES

The following abbreviations are used:

PDMS : Plasma Desorption Mass Spectrometry.

HPLC : High Performance Liquid Chromatography.

amu : atomic mass units.

DMF : N,N-dimethylformamide.

NMP : N-methyl-2-pyrrolidone.

EDPA : N-ethyl-N,N-diisopropylamine.

Myr-ONSu: tetradecanoic acid 2,5-dioxo-pyrrolidin-1-yl ester

TFA : Trifluoroacetic Acid

Analytical

Plasma Desorption Mass Spectrometry

Sample preparation:

The sample is dissolved in 0.1 % TFA/EtOH (1:1) at a concentration of 1 µg/µl. The sample solution (5-10 µl) is placed on a nitrocellulose target (Bio-ion AB, Uppsala, Sweden) and allowed to adsorb to the target surface for 2 minutes. The target is subsequently rinsed with 2x25 µl 0.1 % TFA and spin-dried. Finally, the nitrocellulose target is placed in a target caroussel and introduced into the mass spectrometer.

MS analysis:

Mass spectrometric analysis is carried out using a Bio-ion 20 time-of flight instrument (Bio-ion Nordic AB, Uppsala, Sweden). An acceleration voltage of 15 kV is applied and molecular ions formed by bombardment of the nitrocellulose surface with 252-Cf fission fragments are accelerated towards a stop detector. The resulting time-of-flight spectrum is calibrated into a true mass spectrum using the H^+ and NO^+ ions at m/z 1 and 30, respectively. Mass spectra are generally accumulated for $1.0x10^6$ fission events corresponding to 15-20 minutes. Resulting assigned masses all correspond to isotopically averaged molecular masses. The accuracy of mass assignment is generally better than 0.1 %.

Example 1

Synthesis of $Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37).

The title compound was synthesized from GLP-1(7-37). A mixture of GLP-1(7-37) (25 mg, 7.45 μm), EDPA (26.7 mg, 208 μm), NMP (520 μl) and water (260 μl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (2.5 mg, 7.67 μm) in NMP (62.5 μl), the reaction mixture was gently shaken for 5 min. at room temperature and then allowed to stand for 20 min. An additional amount of Myr-ONSu (2.5 mg, 7.67 μm) in NMP (62.5 μl) was added and the resulting mixture gently shaken for 5 min. After a total reaction time of 40 min. the reaction was quenched by the addition of a solution of glycine (125 mg, 166 μm) in 50% aqueous ethanol (12.5 ml). The title compound was isolated from the reaction mixture by HPLC using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system, yield: 1.3 mg (corresponding to 4.9% of the theoretical yield). The column was heated to 65° C and the acetonitrile gradient was 0-100% in 60 minutes. The isolated product was analyzed by PDMS and the m/z value for the protonated molecular ion was found to be 3567.9±3. The resulting molecular weight is thus 3566.9±3 amu (theoretical value: 3565.9 amu). The position of acylation (Lys26) was verified by enzymatic cleavage of the title compound with Staphylococcus aureus V8 protease and subsequent mass determination of the peptide fragments by PDMS.

In addition to the title compound two other GLP-1 derivatives were isolated from the reaction mixture by using the same chromatographic column and a more shallow gradient (35-38% acetonitrile in 60 minutes), see Examples 2 and 3.

Example 2

Synthesis of $Lys^{34}(N^{\varepsilon}$-tetradecanoyl)GLP-1(7-37).

The title compound was isolated by HPLC from the reaction mixture described in Example 1. PDMS analysis yielded a protonated molecular ion at m/z 3567.7±3. The molecular weight is thus found to be 3566.7±3 amu (theoretical value: 3565.9 amu). The acylation site was determined on the basis of the fragmentation pattern.

Example 3

Synthesis of $Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-37).

The title compound was isolated by HPLC from the reaction mixture described in Example 1. PDMS analysis yielded a protonated molecular ion at m/z 3778.4±3. The molecular weight is thus found to be 3777.4±3 amu (theoretical value: 3776.1 amu).

Example 4

Synthesis of Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}GLP-1(7-37).

The title compound was synthesized from Arg^{34}GLP-1(7-37). A mixture of Arg^{34} GLP-1(7-37) (5 mg, 1.47 μm), EDPA (5.3 mg, 41.1 μm), NMP (105 μl) and water (50 μl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (0.71 mg, 2.2 μm) in NMP (17.8 μl), the reaction mixture was gently shaken for 5 min. at room temperature and then allowed to stand for 20 min. After a total reaction time of 30 min. the reaction was quenched by the addition of a solution of glycine (25 mg, 33.3 μm) in 50% aqueous ethanol (2.5 ml). The reaction mixture was purified by HPLC as described in Example 1. PDMS analysis yielded a protonated molecular ion at m/z 3594.9±3. The molecular weight is thus found to be 3593.9±3 amu (theoretical value: 3593.9 amu).

Example 5

Synthesis of Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-37).

The title compound was synthesized from Gly^{8},$Arg^{26,34}$,Lys^{36}-GLP-1(7-37) which was

purchased from QCB. A mixture of Gly^{8},$Arg^{26,34}$,Lys^{36}-GLP-1(7-37) (1.3 mg, 0.39 μm), EDPA (1.3 mg, 10 μm), NMP (125 μl) and water (30 μl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (0.14 mg, 0.44 μm) in NMP (3.6 μl), the reaction mixture was gently shaken for 15 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (0.1 mg, 1.33 μm) in 50% aqueous ethanol (10 μl). The reaction mixture was purified by HPLC.

CLAIMS

1. A GLP derivative comprising a lipophilic substituent attached to any one amino acid residue with the proviso that only if the substituent has an ω-carboxylic acid group or is an alkyl group can it be attached to the N-terminal or C-terminal amino acid residue of the parent polypeptide.

2. A GLP derivative according to claim 1, wherein the lipophilic substituent comprises from 4 to 40 carbon atoms, more preferred from 8 to 25.

3. A GLP derivative according to claim 1, wherein said lipophilic substituent is attached to said amino acid in such a way that a carboxyl group of the lipophilic substituent forms an amide bond with an amino group of the amino acid.

4. A GLP derivative according to claim 1, wherein said lipophilic substituent is attached to said amino acid in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid.

5. A GLP derivative according to claim 1, wherein the lipophilic substituent is attached to the parent polypeptide by means of a spacer.

6. A GLP derivative according to claim 5, wherein the spacer is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, preferably two methylene groups which form a bridge between an amino group of the parent polypeptide and an amino group of the lipophilic substituent.

7. A GLP derivative according to claim 5, wherein the spacer is an amino acid residue except Cys, or a dipeptide such as Gly-Lys.

8. A GLP derivative according to claim 7, wherein a carboxyl group of the parent polypeptide forms an amide bond with an amino group of Lys or a dipeptide containing a Lys residue, and the other amino group of the Lys or a dipeptide containing a Lys residue forms an amide bond with a carboxyl group of the lipophilic substituent.

9. A GLP derivative according to claim 7, wherein an amino group of the parent polypeptide forms an amide bond with a carboxylic group of the amino acid or dipeptide spacer, and an amino group of the amino acid or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

10. A GLP derivative according to claim 7, wherein a carboxyl group of the parent polypeptide forms an amide bond with an amino group of the amino acid or dipeptide spacer, and the carboxyl group of the amino acid or dipeptide spacer forms an amide bond with an amino group of the lipophilic substituent.

11. A GLP derivative according to claim 7, wherein a carboxyl group of the parent polypeptide forms an amide bond with an amino group of Asp or Glu, or a dipeptide containing an Asp or Glu residue, and a carboxyl group of the spacer forms an amide bond with an amino group of the lipophilic substituent.

12. A GLP derivative according to any of claims 1-4, wherein the lipophilic substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

13. A GLP derivative according to any of claims 1-4, wherein the lipophilic substituent is an straight-chain or branched alkyl group.

14. A GLP derivative according to any of claims 1-5, 8 and 9 wherein the lipophilic substituent is the acyl group of a straight-chain or branched fatty acid.

15.A GLP derivative according to claim 14 wherein the acyl group is selected from the group comprising $CH_3(CH_2)_nCO$-, wherein n is 4 to 38, preferably $CH_3(CH_2)_6CO$-, $CH_3(CH_2)_8CO$-, $CH_3(CH_2)_{10}CO$-, $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-.

16.A GLP derivative according to any of claims 1-5, 8 and 9 wherein the lipophilic substituent is an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid.

17.A GLP derivative according to claim 16 wherein the acyl group is selected from the group comprising $HOOC(CH_2)_mCO$-, wherein m is 4 to 38, preferably $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- and $HOOC(CH_2)_{22}CO$-.

18.A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $CH_3(CH_2)_p((CH_2)_qCOOH)CHNH\text{-}CO(CH_2)_2CO$-, wherein p and q are integers and p+q is an integer of from 8 to 40, preferably from 12 to 35.

19.A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophlic substituent is a group of the formula $CH_3(CH_2)_rCO\text{-}NHCH(COOH)(CH_2)_2CO$-, wherein r is an integer of from 10 to 24.

20.A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $CH_3(CH_2)_sCO\text{-}NHCH((CH_2)_2COOH)CO$-, wherein s is an integer of from 8 to 24.

21.A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $COOH(CH_2)_tCO$- wherein t is an integer of from 8 to 24.

22.A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_uCH_3$, wherein u is an integer of

from 8 to 18.

23. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula -NHCH(COOH)$(CH_2)_4$NH-COCH(($(CH_2)_2$COOH)NH-CO$(CH_2)_w CH_3$, wherein w is an integer of from 10 to 16.

24. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula -NHCH(COOH)$(CH_2)_4$NH-CO$(CH_2)_2$CH(COOH)NH-CO$(CH_2)_x CH_3$, wherein x is an integer of from 10 to 16.

25. A GLP derivative according to any of claims 1-5, 8 and 9, wherein the lipophilic substituent is a group of the formula -NHCH(COOH)$(CH_2)_4$NH-CO$(CH_2)_2$CH(COOH)NHCO$(CH_2)_y CH_3$, wherein y is zero or an integer of from 1 to 22.

26. A GLP derivative according to any of the preceding claims which has one lipophilic substituent.

27. A GLP derivative according to any one of claims 1-25 which has two lipophilic substituents.

28. A GLP derivative according to any of claims 1-27, wherein the parent polypeptide is selected from the group comprising GLP-1(1-45) or an analogue or a fragment thereof.

29. A GLP-1 derivative according to claim 28, selected from the group comprising GLP-1(7-35), GLP-1(7-36), GLP-1(7-36)amide, GLP-1(7-37), GLP-1(7-38), GLP-1(7-39), GLP-1(7-40) and GLP-1(7-41) and an analogue thereof.

30. A GLP-1 derivative according to claim 28, selected from the group comprising GLP-1(1-35), GLP-1(1-36), GLP-1(1-36)amide, GLP-1(1-37), GLP-1(1-38), GLP-1(1-39), GLP-1(1-40) and GLP-1(1-41) and an analogue thereof.

31. A GLP-1 derivative according to any of the claims 28-30 wherein the designation analogue comprises derivatives wherein a total of up to fifteen, preferably up to ten amino acid residues have been exchanged with any α-amino acid residue.

32. A GLP-1 derivative according to any of the preceding claims wherein the parent polypeptide is selected from the group comprising Arg^{26}-GLP-1(7-37), Arg^{34}-GLP-1(7-37), Lys^{36}-GLP-1(7-37), $Arg^{26,34}$,Lys^{36}-GLP-1(7-37), $Arg^{26,34}$,Lys^{39}-GLP-1(7-39), $Arg^{26,34}$,Lys^{40}-GLP-1(7-40), Arg^{26},Lys^{36}-GLP-1(7-37), Arg^{34},Lys^{36}-GLP-1(7-37), Arg^{26},Lys^{39}-GLP-1(7-39), Arg^{34},Lys^{40}-GLP-1(7-40), $Arg^{26,34}$,$Lys^{36,39}$-GLP-1(7-39), $Arg^{26,34}$,$Lys^{36,40}$-GLP-1(7-40), Gly^{8},Arg26-GLP-1(7-37), Gly^{8},Arg^{34}-GLP-1(7-37), Gly^{8},Lys^{36}-GLP-1(7-37), Gly^{8},$Arg^{26,34}$,Lys^{36}-GLP-1(7-37), Gly^{8},$Arg^{26,34}$,Lys^{39}-GLP-1(7-39), Gly^{8},$Arg^{26,34}$,Lys^{40}-GLP-1(7-40), Gly^{8},Arg^{26},Lys^{36}-GLP-1(7-37), Gly^{8},Arg^{34},Lys^{36}-GLP-1(7-37), Gly^{8},Arg^{26},Lys^{39}-GLP-1(7-39), Gly^{8},Arg^{34},Lys^{40}-GLP-1(7-40), Gly^{8},$Arg^{26,34}$,$Lys^{36,39}$-GLP-1(7-39)and Gly^{8},$Arg^{26,34}$,$Lys^{36,40}$-GLP-1(7-40).

33. A GLP-1 derivative according to claim 28, which is selected from the group comprising

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-37);
Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-37);
Arg^{26},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);
$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);
$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);
$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-38);
Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);
Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);
Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-38);
Arg^{26},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-39);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-39);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-36);

$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-36);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-36);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-35);

$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-35);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-35);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-36)amide;

$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-37);

Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-37);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-38);

Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-38);

$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-38);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-38);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-39);

Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-39);

$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-39);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-39);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-tetradecanoyl),Arg^{34}-GLP-1(7-40);

$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Gly^{8},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-38);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-39);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(ω-carboxynonadecanoyl)),Arg^{34}-GLP-1(7-40);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Gly^{8},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36)amide;

Arg^{26},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

Gly^{8},Arg^{26},$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-37);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-37);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-37);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-37);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-38);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-38);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-38);

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-38);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-38);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-38);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-39);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-39);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-39);

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-39);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-39);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-39);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(7-deoxycholoyl)),Arg^{34}-GLP-1(7-40);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-40);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-40);

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-40);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-40);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36);

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-35);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-35);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-35);

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-35);

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-35);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(choloyl)),Arg^{34}-GLP-1(7-37);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(choloyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

Gly^{8},Arg^{26},$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(choloyl)),Arg^{34}-GLP-1(7-38);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(choloyl))Arg^{34}-GLP-1(7-38);

$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

Gly^{8},$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-38);

$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-38);

Gly^{8},$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-38);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Arg^{26},$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-38);

Gly^{8},Arg^{26},$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-(choloyl)),Arg^{34}-GLP-1(7-39);

Gly^{8},$Lys^{26}(N^{\varepsilon}$-(choloyl))Arg^{34}-GLP-1(7-39);

$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(choloyl))-GLP-1(7-39);

Gly^{8},$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-(choloyl))-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-39);

$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(choloyl)),Arg^{34}-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-40);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-40);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(choloyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-35);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8},$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(lithocholoyl)),Arg^{34}-GLP-1(7-37);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(lithocholoyl)),Arg^{34}-GLP-1(7-38);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))Arg^{34}-GLP-1(7-38);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(lithocholoyl)),Arg^{34}-GLP-1(7-39);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))Arg^{34}-GLP-1(7-39);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Gly^{8},Arg^{26},Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(lithocholoyl)),Arg^{34}-GLP-1(7-40);

Gly^{8},Lys^{26}(N^{ε}-(lithocholoyl))Arg^{34}-GLP-1(7-40);

$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-40) and

Gly^{8},$Arg^{26,34}$,Lys^{36}(N^{ε}-(lithocholoyl))-GLP-1(7-40).

34.A GLP derivative according to any of claims 1-26, wherein the parent polypeptide is selected from the group comprising GLP-2(1-35) or an analogue or a fragment thereof.

35.A GLP-2 derivative according to claim 34, selected from the group comprising GLP-2(1-30), GLP-2(1-31), GLP-2(1-32), GLP-2(1-33), GLP-2(1-34) and GLP-2(1-35).

36.A GLP-2 derivative according to any of the claims 34 and 35 wherein the designation analogue comprises derivatives wherein a total of up to ten amino acid residues have been exchanged with any α-amino acid residue.

37.A GLP-2 derivative according to any of the claims 1-27 and 34-36 wherein the parent polypeptide is selected from the group comprising Lys^{20}-GLP-2(1-33), Lys^{20},Arg^{30}-GLP-2(1-33), Arg^{30},Lys^{35}-GLP-2(1-35), $Arg^{30,35}$,Lys^{20}-GLP-2(1-35), Arg^{35}-GLP-2(1-35), Arg^{30},Lys^{34}-GLP-2(1-34).

38.A GLP-2 derivative according to claim 34, which is selected from the group consisting of

$Lys^{20}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-33);
$Lys^{20,30}$-bis(N^{ε}-tetradecanoyl)-GLP-2(1-33);
$Lys^{20}(N^{\varepsilon}$-tetradecanoyl),Arg^{30}-GLP-2(1-33);
Arg^{30},$Lys^{35}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-35);
$Arg^{30,35}$,$Lys^{20}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-35);
Arg^{35},$Lys^{30}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-35);
Arg^{30},$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-2(1-34);
$Lys^{20}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-2(1-33);
$Lys^{20,30}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-2(1-33);
$Lys^{20}(N^{\varepsilon}$-(ω-carboxynonadecanoyl)),Arg^{30}-GLP-2(1-33);
Arg^{30},$Lys^{35}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-2(1-35);
$Arg^{30,35}$,$Lys^{20}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-2(1-35);
Arg^{35},$Lys^{30}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-2(1-35); and

Arg^{30},Lys^{34}(N^{ε}-(ω-carboxynonadecanoyl))-GLP-2(1-34).

39. A pharmaceutical composition comprising a GLP derivative according to any of the preceding claims and a pharmaceutically acceptable vehicle or carrier.

40. Use of a GLP derivative according to any of the preceding claims for the preparation of a medicament with protracted effect.

41. Use of a GLP-1 derivative according to any of claims 28-33 for the preparation of a medicament with protracted effect for the treatment of non-insulin dependent diabetes mellitus.

42. Use of a GLP-1 derivative according to any of claims 28-33 for the preparation of a medicament with protracted effect for the treatment of insulin dependent diabetes mellitus.

43. Use of a GLP-1 derivative according to any of claims 28-33 for the preparation of a medicament with protracted effect for the treatment of obesity.

44. Use of a GLP-2 derivative according to any of claims 36-40 for the preparation of a medicament with protracted effect for the treatment of obesity.

45. Use of a GLP-2 derivative according to any of claims 36-40 for the preparation of a medicament with protracted effect for the treatment of small bowel syndrome.

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ABSTRACT

GLP DERIVATIVES

Derivatives of GLP-1 and GLP-2 and analogues thereof. having a lipophilic substituent have interesting pharmacological properties, in particular they have a more protracted profile of action than the parent peptides.